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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,443	XIE ET AL.	
	Examiner	Art Unit	
	STEPHANIE K. MUMMERT	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-13,18-25 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-13,18-25 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/14/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on July 20, 2009 is acknowledged and has been entered. Claims 1 and 21 have been amended. Claims 4-5, 14-17, 26-27, 29-36 have been canceled. Claims 1-3, 6-13, 18-25, 28 are pending.

Claims 1-3, 6-13, 18-25, 28 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made FINAL as necessitated by Amendment.

New Grounds of Rejection

Information Disclosure Statement

The information disclosure statement (IDS) submitted on May 14, 2009 was filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Correction of Inventorship

See MPEP 201.03 for details regarding correction of inventorship

The request to correct the inventorship of this nonprovisional application under 37 CFR 1.48(a) is deficient because:

An oath or declaration by each actual inventor or inventors listing the entire inventive entity has not been submitted.

A 37 CFR 3.73(b) submission has not been received to support action by the assignee. It lacks the required fee under 37 CFR 1.17(i).

The statement of facts by an inventor or inventors to be added or deleted does not explicitly state that the inventorship error occurred without deceptive intent on his or her part or cannot be construed to so state.

A 37 CFR 3.73(b) submission has not been received to support action by the assignee.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6-9, 12-13, 18, 20-25, 28 and 37 are rejected under 35 U.S.C. 103(a) as being obvious over Dauer et al. (Biotechnology and Bioengineering, 1991, vol. 37, p. 1021-1028) in view of Inuma et al. (Int. J. Cancer, 2000, vol. 89, p. 337-344) and Grevelding et al. (Nucleic Acids Research, 1996, 24(20), p. 4100-4101). Dauer teaches a method of isolating cells using magnetic particles (Abstract).

With regard to claim 1, Dauer teaches a process for amplifying a nucleic acid of a target cell or virus, which process comprises:

a) contacting a sample containing or suspected of containing a target cell or virus with a magnetic microbead (p. 1024, col. 2, where baker's yeast were the target cells and where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe2O3); see Table 1);

b) allowing said target cell or virus, if present in said sample, to bind to said magnetic microbead nonspecifically or with low specificity to form a conjugate between said target cell or virus and said magnetic microbead (Figure 6, where the process of mixing, binding and separation are depicted; p. 1025, col. 2, where the magnetic particles and the yeast are incubated together for 10 minutes, and where the pH is used to control binding to the particles and then release of the particles and where the contact is not mediated by a biomolecule and therefore is non-specific, see also Table 1);

c) separating said conjugate from other undesirable constituents via a magnetic force to isolate said target cell or virus from said sample (Figure 6, E, where the conjugate between the magnetic particle and the cells are separated from the sample).

With regard to claim 37, Dauer teaches a process for amplifying a nucleic acid of a cell, which process comprises:

a) contacting a sample containing or suspected of containing a cell with a magnetic microbead (p. 1024, col. 2, where baker's yeast were the target cells and where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe2O3); see Table 1);

b) allowing said cell, if present in said sample, to bind to said magnetic microbead nonspecifically or with low specificity to form a conjugate between said cell and said magnetic microbead (Figure 6, where the process of mixing, binding and separation are depicted; p. 1025, col. 2, where the magnetic particles and the yeast are incubated together for 10 minutes, and where the pH is used to control binding to the particles and then release of the particles and where the contact is not mediated by a biomolecule and therefore is non-specific, see also Table 1); and

c) separating said conjugate from other undesirable constituents via a magnetic force to isolate said leukocyte cell from said sample (Figure 6, E, where the conjugate between the magnetic particle and the cells are separated from the sample).

With regard to claim 6, Dauer teaches an embodiment of claim 1, wherein the magnetic microbead comprises a magnetizable substance selected from the group consisting of a paramagnetic substance, a ferromagnetic substance and a ferrimagentic substance (p. 1024, col. 2, where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe2O3); see Table 1).

With regard to claim 7, Dauer teaches an embodiment of claim 6, wherein the magnetizable substance comprises a metal composition (p. 1024, col. 2, where baker's yeast were the target cells and where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe2O3); see Table 1).

With regard to claim 8, Dauer teaches an embodiment of claim 7, wherein the metal composition is a transition metal composition or an alloy thereof (p. 1024, col. 2, where the

magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe2O3); see Table 1).

With regard to claim 9, Dauer teaches an embodiment of claim 8, wherein the transition metal is selected from the group consisting of iron, nickel, copper, cobalt, manganese, tantalum, zirconium and cobalt- tantalum-zirconium (CoTaZr) alloy (p. 1024, col. 2, where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe2O3); see Table 1).

With regard to claim 12-13, Dauer teaches an embodiment of claim 1, wherein the magnetic microbead is untreated or modified with an organic molecule such as hydroxyl, carboxyl or epoxy (Table 1, p. 1024, col. 2, where the magnetic particle is not coated with a biomolecule or other affinity group).

With regard to claim 18, Dauer teaches an embodiment of claim 1, which further comprises washing the separated conjugate to remove the undesirable constituents before applying separated conjugate to a nucleic acid amplification system (p. 1021, col. 2, where the cells are washed with water and air).

With regard to claim 20, Dauer teaches an embodiment of claim 1, which is completed within a time ranging from about 0.5 minute to about 30 minutes (p. 1025, col. 2, where the magnetic particles and the yeast are incubated together for 10 minutes).

With regard to claim 22, Dauer teaches an embodiment of claim 1, which is conducted in the absence of a precipitation or centrifugation procedure (p. 1025, where the magnetic cell composition is passed through a filter, which is highly magnetized to attract and capture magnetic entities, see p. 1021).

With regard to claim 23, Dauer teaches an embodiment of claim 1, which is conducted in the absence of a poisonous agent (p. 1025, where the magnetic cell composition is passed through a filter, which is highly magnetized to attract and capture magnetic entities, see p. 1021).

With regard to claim 24, Dauer teaches an embodiment of claim l, which is conducted at an ambient temperature ranging from about 0°C to about 35°C without temperature control (p. 1025, col. 1, where the temperature is set at 25 +/- 2oC).

Regarding claim 1 and 37, Dauer does not explicitly teach that the target cell is a leukocyte. Inuma teaches that leukocytes can be specifically targeted by magnetic beads comprising antibodies (p. 337, col. 2). Regarding claim 37, Dauer does not teach that the sample is obtained from whole blood.

With regard to claim 1, Inuma teaches a leukocyte target cell (p. 337, col. 2, where 'anti-CD45 Mab-conjugated microbeads... bind to a common antiden of leukocytes').

With regard to claim 37, Inuma teaches a) contacting a whole blood sample containing or suspected of containing a leukocyte cell with a magnetic microbead (p. 337, col. 2, where 'anti-CD45 Mab-conjugated microbeads... bind to a common antiden of leukocytes'); and said leukocyte cells (p. 337, col. 2, where 'anti-CD45 Mab-conjugated microbeads... bind to a common antiden of leukocytes').

Regarding claim 1 and 37, Dauer does not explicitly teach that the cells can be applied to an amplification system.

With regard to claim 1 and 37, Grevelding teaches a method comprising d) applying said separated conjugate to a nucleic acid amplification system to amplify a nucleic acid from said target cell or virus, wherein said process does not comprise a step of lysing said target cell or

virus to release said nucleic acid prior to applying said separated conjugate to said nucleic acid amplification system (Abstract, p. 4100, col. 1, where the technique of PCR is applied to whole organisms and has been applied to yeast and bacteria).

With regard to claim 2, Grevelding teaches an embodiment of claim 1, wherein the sample is a clinical sample comprising cells from the organism (p. 4100, col. 1, where the cells include S. mansoni, a blood fluke that infects humans).

With regard to claim 3, Grevelding teaches an embodiment of claim 1, wherein the sample is selected from the group consisting of serum, plasma, whole blood, sputum, cerebral spinal fluid, amniotic fluid, urine, gastrointestinal contents, hair, saliva, sweat, gum scrapings, marrow, tissue and cell culture (p. 4100, col. 1, where the cells include S. mansoni, a blood fluke that infects humans).

With regard to claim 21, Grevelding teaches an embodiment of claim 1, which is conducted in an eppendorf tube (p. 4100, where the process of setting up the reactions occurs in an eppendorf tube).

With regard to claim 25, Grevelding teaches an embodiment of claim 1, wherein the sample volume ranges from about 5 ul to about 50 ul (p. 4100, col. 2, where the reactions were carried out in a total volume of 25 ul).

With regard to claim 28, Grevelding teaches an embodiment of claim 1, wherein the nucleic acid amplification system is selected from the group consisting of polymerase chain reaction (PCR), ligase chain reaction (LCR), nucleic acid sequence-based amplification (NASBA), strand displacement amplification (SDA) and transcription-medicated amplification (TMA) (p. 4100, where the amplification was PCR; see legend to Figure 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have analyzed the target cells of Inuma using the method of separation taught by Dauer to arrive at the claimed invention with a reasonable expectation for success. As taught by Inuma, "prepared cells were resuspended in 80 μl of BSA-PBS mixed with 20 μl of CD45 microbeads for 15 min at 4°C and passed down the MACS column" (p. 338, col. 1). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have analyzed the target cells of Inuma using the method of separation taught by Dauer to arrive at the claimed invention with a reasonable expectation for success. Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the method of Dauer to include further analysis of the captured and released cells using PCR amplification as taught by Grevelding to arrive at the claimed invention with a reasonable expectation for success. As taught by Grevelding, "recently protocols were introduced that allow PCR amplification without DNA extraction" and "we show that PCR amplification is possible from whole, undissected larvae and adults of the fruitfly Drosophila melanogaster and the blood fluke, Schistosoma mansoni without preceeding DNA isolation." Regarding the applicability of the method to other types of cells, Grevelding teaches "Since it worked both with an organism covered by a tegument as well as one surrounded by a chitineous cuticle, it is expected that it should also be applicable for a variety of other eukaryotic organisms" (p. 4101, col. 1). While Grevelding teaches isolation from whole organisms, the technique of amplification directly from cells without prior DNA extraction is clearly supported by the teachings of Grevelding. Therefore, one of ordinary skill in the art would have been motivated to have adjusted the method of Dauer to include further analysis of the captured and

released cells using PCR amplification as taught by Grevelding to arrive at the claimed invention with a reasonable expectation for success.

Claims 5 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dauer in view of Inuma and Grevelding as applied to claims 1-3, 6-9, 12-13, 18, 20-25, 28 and 37 above, and further in view of Lopez-Sabater et al. (Letters in Applied Microbiology, 1997, vol. 24, p. 101-104). Dauer teaches a method of isolating cells using magnetic particles (Abstract).

Dauer in view of Inuma and Grevelding teaches all of the limitations of claims 1-3, 6-9, 12-13, 18, 20-25, 28 and 37 as recited in the 103 rejection stated above. However, Dauer does not teach removing cells suspected of containing a virus before contacting the sample with microbeads. Lopez-Sabater teaches a method for the magnetic immunoseparation for detection of viral sequences by PCR (Abstract).

With regard to claim 5, Lopez-Sabater teaches an embodiment of claim 1, wherein the target virus is an eucaryotic cell virus or a bacteriophage (p. 102, col. 1, where the cells were innoculated with virus and the cells are eucaryotic and therefore the target virus is a eucaryotic cell virus).

With regard to claim 29, Lopez-Sabater teaches an embodiment of claim 1, which further comprises removing cells from a sample containing or suspected of containing a target virus or bacteriophage before contacting the sample with a magnetic microbead (p. 102, col. 1, 'recovery' heading, where the oyster cells were diced and homogenized, therefore the cells were removed before contacting with a magnetic microbead).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the technique of homogenization of a sample suspected of containing a virus as taught by Lopez-Sabater to the method of isolation and analysis taught by Dauer to arrive at the claimed invention with a reasonable expectation for success. As taught by Lopez-Sabater, "samples (20g) of shucked American oyster… were inoculated with levels of HAV ranging from 10 to 10^3 pfu" and "after 1 hour at room temperature, artificially contaminated oysters were diced with sterile scissors" and subsequently homogenized (p. 102, col. 1). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have applied the technique of homogenization of a sample suspected of containing a virus as taught by Lopez-Sabater to the method of isolation and analysis taught by Dzieglewska to arrive at the claimed invention with a reasonable expectation for success.

Claim 10 is rejected under 35 U.S.C. 103(a) as being obvious over Dauer in view of Inuma and Grevelding as applied to claims 1-3, 6-9, 12-13, 18, 20-25, 28 and 37 and further in view of Ughelstad et al. (WO83/03920; November 1983). Dauer teaches a method of isolating cells using magnetic particles (Abstract).

Regarding magnetic beads, Dauer teaches that the magnetic particles are ferromagnetic. Ughelstad teaches the details of the process of forming magnetic particles (Abstract).

With regard to claim 10, Ughelstad teaches an embodiment of claim 7, wherein the metal composition is Fe304 (p. 9, where the metal comprises Fe3O4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the specific teachings of Ughelstad to the particles of Dauer

to arrive at the claimed invention with a reasonable expectation for success. As taught by Dauer, "The magnetic seed is a ferromagnetic γ-iron oxide (γ-Fe2O3) or maghemite" (p. 1024, col. 2). Ughelstad teaches wherein the method composition comprises Fe3O4 specifically (see p. 9). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have applied the specific teachings of Ughelstad to the particles of Dzieglewska to arrive at the claimed invention with a reasonable expectation for success.

Claims 1-3, 6-9, 12-13, 18, 20-25, 28 and 38 are rejected under 35 U.S.C. 103(a) as being obvious over Dauer et al. (Biotechnology and Bioengineering, 1991, vol. 37, p. 1021-1028) in view of O'Neill et al. (US Patent 6,187,546; February 2001) and Grevelding et al. (Nucleic Acids Research, 1996, 24(20), p. 4100-4101). Dauer teaches a method of isolating cells using magnetic particles (Abstract).

With regard to claim 1, Dauer teaches a process for amplifying a nucleic acid of a target cell or virus, which process comprises:

a) contacting a sample containing or suspected of containing a target cell or virus with a magnetic microbead not comprising a biomolecule that binds to said target cell or virus with high specificity (p. 1024, col. 2, where baker's yeast were the target cells and where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe2O3); see Table 1);

b) allowing said target cell or virus, if present in said sample, to bind to said magnetic microbead to form a conjugate between said target cell or virus and said magnetic microbead (Figure 6, where the process of mixing, binding and separation are depicted; p. 1025, col. 2,

where the magnetic particles and the yeast are incubated together for 10 minutes, and where the pH is used to control binding to the particles and then release of the particles);

c) separating said conjugate from other undesirable constituents via a magnetic force to isolate said target cell or virus from said sample (Figure 6, E, where the conjugate between the magnetic particle and the cells are separated from the sample),

wherein said biomolecule is selected from the group consisting of an antibody, an amino acid, a peptide, a protein, a nucleoside, a nucleotide, an oligonucleotide, a nucleic acid, a vitamin, a monosaccharide, an oligosaccharide, a carbohydrate, a lipid and a complex thereof (Table 1, p. 1024, col. 2, where the magnetic particle is not coated with a biomolecule or other affinity group).

With regard to claim 38, Dauer teaches a process for amplifying a nucleic acid of an epithelial cell, which process comprises:

a) contacting a sample containing or suspected of containing a cell with a magnetic microbead (p. 1024, col. 2, where baker's yeast were the target cells and where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe_2O_3); see Table 1);

b) allowing said cell, if present in said sample, to bind to said magnetic microbead nonspecifically or with low specificity to form a conjugate between said cell and said magnetic microbead (Figure 6, where the process of mixing, binding and separation are depicted; p. 1025, col. 2, where the magnetic particles and the yeast are incubated together for 10 minutes, and where the pH is used to control binding to the particles and then release of the particles); and

c) separating said conjugate from other undesirable constituents via a magnetic force to

isolate said cell from said sample (Figure 6, E, where the conjugate between the magnetic particle and the cells are separated from the sample).

With regard to claim 6, Dauer teaches an embodiment of claim 1, wherein the magnetic microbead comprises a magnetizable substance selected from the group consisting of a paramagnetic substance, a ferromagnetic substance and a ferrimagentic substance (p. 1024, col. 2, where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe2O3); see Table 1).

With regard to claim 7, Dauer teaches an embodiment of claim 6, wherein the magnetizable substance comprises a metal composition (p. 1024, col. 2, where baker's yeast were the target cells and where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe2O3); see Table 1).

With regard to claim 8, Dauer teaches an embodiment of claim 7, wherein the metal composition is a transition metal composition or an alloy thereof (p. 1024, col. 2, where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe2O3); see Table 1).

With regard to claim 9, Dauer teaches an embodiment of claim 8, wherein the transition metal is selected from the group consisting of iron, nickel, copper, cobalt, manganese, tantalum, zirconium and cobalt- tantalum-zirconium (CoTaZr) alloy (p. 1024, col. 2, where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe2O3); see Table 1).

With regard to claim 12-13, Dauer teaches an embodiment of claim 1, wherein the magnetic microbead is untreated or modified with an organic molecule such as hydroxyl,

carboxyl or epoxy (Table 1, p. 1024, col. 2, where the magnetic particle is not coated with a biomolecule or other affinity group).

With regard to claim 18, Dauer teaches an embodiment of claim 1, which further comprises washing the separated conjugate to remove the undesirable constituents before applying separated conjugate to a nucleic acid amplification system (p. 1021, col. 2, where the cells are washed with water and air).

With regard to claim 20, Dauer teaches an embodiment of claim 1, which is completed within a time ranging from about 0.5 minute to about 30 minutes (p. 1025, col. 2, where the magnetic particles and the yeast are incubated together for 10 minutes).

With regard to claim 22, Dauer teaches an embodiment of claim 1, which is conducted in the absence of a precipitation or centrifugation procedure (p. 1025, where the magnetic cell composition is passed through a filter, which is highly magnetized to attract and capture magnetic entities, see p. 1021).

With regard to claim 23, Dauer teaches an embodiment of claim 1, which is conducted in the absence of a poisonous agent (p. 1025, where the magnetic cell composition is passed through a filter, which is highly magnetized to attract and capture magnetic entities, see p. 1021).

With regard to claim 24, Dauer teaches an embodiment of claim l, which is conducted at an ambient temperature ranging from about 0°C to about 35°C without temperature control (p. 1025, col. 1, where the temperature is set at 25 +/- 2oC).

Regarding claim 38, Dauer does not explicitly state that the sample comprises saliva or that the target cell comprises an epithelial cell. Miyashita teaches analysis of epithelial cells in saliva samples (Abstract).

With regard to claim 38, O'Neill teaches a saliva sample containing or suspected of containing an epithelial cell (col. 20, where epithelial cells are exfoliated into saliva or sputum), wherein the epithelial cell is enriched and isolated by binding to a magnetic particle (col. 20, lines 32-35, where epithelial cells are enriched using magnetic particle sorting).

Regarding claims 1 and 38, neither Dauer or O'Neill explicitly teach that the cells can be applied to an amplification system.

With regard to claim 1, Grevelding teaches a method comprising d) applying said separated conjugate to a nucleic acid amplification system to amplify a nucleic acid from said target cell or virus, wherein said process does not comprise a step of lysing said target cell or virus to release said nucleic acid prior to applying said separated conjugate to said nucleic acid amplification system (Abstract, p. 4100, col. 1, where the technique of PCR is applied to whole organisms and has been applied to yeast and bacteria).

With regard to claim 38, Grevelding teaches a method comprising d) applying said separated conjugate to a nucleic acid amplification system to amplify a nucleic acid from said target cell or virus (Abstract, p. 4100, col. 1, where the technique of PCR is applied to whole organisms and has been applied to yeast and bacteria).

With regard to claim 2, Grevelding teaches an embodiment of claim 1, wherein the sample is a clinical sample comprising cells from the organism (p. 4100, col. 1, where the cells include S. mansoni, a blood fluke that infects humans).

With regard to claim 3, Grevelding teaches an embodiment of claim 1, wherein the sample is selected from the group consisting of serum, plasma, whole blood, sputum, cerebral spinal fluid, amniotic fluid, urine, gastrointestinal contents, hair, saliva, sweat, gum scrapings,

marrow, tissue and cell culture (p. 4100, col. 1, where the cells include S. mansoni, a blood fluke that infects humans).

With regard to claim 21, Grevelding teaches an embodiment of claim 1, which is conducted in an eppendorf tube (p. 4100, where the process of setting up the reactions occurs in an eppendorf tube).

With regard to claim 25, Grevelding teaches an embodiment of claim 1, wherein the sample volume ranges from about 5 ul to about 50 ul (p. 4100, col. 2, where the reactions were carried out in a total volume of 25 ul).

With regard to claim 28, Grevelding teaches an embodiment of claim 1, wherein the nucleic acid amplification system is selected from the group consisting of polymerase chain reaction (PCR), ligase chain reaction (LCR), nucleic acid sequence-based amplification (NASBA), strand displacement amplification (SDA) and transcription-medicated amplification (TMA) (p. 4100, where the amplification was PCR; see legend to Figure 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the method of Dauer to include further analysis of the captured and released cells using PCR amplification as taught by Grevelding to arrive at the claimed invention with a reasonable expectation for success. As taught by Grevelding, "recently protocols were introduced that allow PCR amplification without DNA extraction" and "we show that PCR amplification is possible from whole, undissected larvae and adults of the fruitfly Drosophila melanogaster and the blood fluke, Schistosoma mansoni without preceeding DNA isolation." Regarding the applicability of the method to other types of cells, Grevelding teaches "Since it worked both with an organism covered by a tegument as well as one surrounded by a

chitineous cuticle, it is expected that it should also be applicable for a variety of other eukaryotic organisms" (p. 4101, col. 1). While Grevelding teaches isolation from whole organisms, the technique of amplification directly from cells without prior DNA extraction is clearly supported by the teachings of Grevelding. Therefore, one of ordinary skill in the art would have been motivated to have adjusted the method of Dauer to include further analysis of the captured and released cells using PCR amplification as taught by Grevelding to arrive at the claimed invention with a reasonable expectation for success.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of Dauer and Grevelding to the analysis and separation of epithelial cells in saliva as taught by O'Neill to arrive at the claimed invention with a reasonable expectation for success. O'Neill teaches, "Exfoliated cells in sputum or saliva or selectively separated" and "iii) After ensuring that the saliva or sputum is diluted enough to reduce its viscosity, immunomagnetic Ber-EP4 beads, of suspension are added to the diluted saliva or sputum and clean-up is performed as for urine" (col. 20, lines 3-5). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the teachings of Dauer and Grevelding to the analysis and separation of epithelial cells in saliva as taught by O'Neill to arrive at the claimed invention with a reasonable expectation for success.

Claims 11 and 19 are rejected under 35 U.S.C. 103(a) as being obvious over Dauer in view of O'Neill and Grevelding as applied to claims 1-3, 6-9, 12-13, 18, 20-25, 28 and 38 and

further in view of Dzieglewska (WO98/51693). Dauer teaches a method of isolating cells using magnetic particles (Abstract).

Regarding claims 11 and 19, Dauer does not teach these specific details regarding the elements of the method as claimed.

With regard to claim 11, Dzieglewska teaches an embodiment of claim 1, wherein the magnetic microbead has a diameter ranging from about 5 to about 50,000 nanometers (p. 9, lines 26-33, where the bead has a diameter of 1-2 um).

With regard to claim 19, Dzieglewska teaches an embodiment of claim 1, which is automated (p. 16, lines 12-14, where the method can be amenable to automation).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Dauer to the include elements of Dzieglewska to arrive at the claimed invention with a reasonable expectation for success. As taught by Dzieglewska, "Representative samples thus include whole blood and blood-derived products such as plasma or buffy coat, urine, faeces, cerebrospinal fluid or any other body fluids, tissues, cell cultures, cell suspensions etc., and also environmental samples such as soil, water, or food samples" (p. 5). Dzieglewska also teaches "The invention is advantageously amenable to automation, particularly if particles, and especially, magnetic particles are used as the support" (p. 16). While Dzieglewska teaches a method that comprises lysis of cells prior to amplification, the elements of the claims represented by Dzieglewska are obvious in combination with the teaching of Dauer and Grevelding. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Dauer and

Grevelding to the include elements of Dzieglewska to arrive at the claimed invention with a reasonable expectation for success.

Response to Arguments

Applicant's arguments with respect to claims 1-13 and 18-29 have been considered but are moot in view of the new ground(s) of rejection.

However, insofar as Applicant's arguments apply to the instantly amended claims, the arguments will be considered. First of all, Applicant indicates that the inventorship of the application needs to be corrected to reflect the correct name, Jing Cheng. The instant inventorship, prior to correction, states Jing Chen.

As noted above, the submission and request for correction of inventorship is insufficient. Next, it is noted, following Applicant's request for clarification and instruction for the correction of inventorship, that MPEP 201.03 provides guidance in this area. Furthermore, as noted in the start of that passage of the MPEP, the correction required for Applicant's case, "37 CFR 1.48(a) is directed at correcting the inventorship in an application where the inventorship was improperly set forth in the executed oath or declaration filed in the application". The typographical error is present in the originally filed oath and declaration. Furthermore, as noted at II - 37 CFR 1.48 Correction of inventorship in a patent application, other than a reissue application, pursuant to 35. U.S.C. 116.

(a) *Nonprovisional application after oath/declaration filed.* If the inventive entity is set forth in error in an executed § 1.63 oath or declaration in a nonprovisional application, and such error arose without any deceptive intention on the part of the person named as an inventor in error or

on the part of the person who through error was not named as an inventor, the inventorship of the nonprovisional application may be amended to name only the actual inventor or inventors. Amendment of the inventorship requires:

(1) A request to correct the inventorship that sets forth the desired inventorship change;

(2) A statement from each person being added as an inventor and from each person being deleted as an inventor that the error in inventorship occurred without deceptive intention on his or her part;

(3) An oath or declaration by the actual inventor or inventors as required by § 1.63 or as permitted by §§ 1.42, 1.43 or § 1.47;

(4) The processing fee set forth in § 1.17(i); and

(5) If an assignment has been executed by any of the original named inventors, the written consent of the assignee (see § 3.73(b) of this chapter).

Next, Applicant traverses the rejection of claims as being obvious over Dauer in view of Grevelding. Applicant argues "neither Dauer nor Grevelding teaches or even suggests non-specific or low-specificity magnetic separation of mammalian cells, particularly leukocytes or epithelial cells". Applicant also states that "neither Dauer nor Grevelding provides any indication that direct PCR amplification would be effective on mammalian cells"

While Applicant's arguments are noted, first of all, it is unclear how Dauer does not teach non-specific separation of cells since the magnetic seeds are not bound with a specific

biomolecule or other binding partner. It is clear from the teaching of Dauer that the magnetic seeds are non-specifically bound to the target cells, regardless of the volume of the cells which are separated. Next, it is noted that while Grevelding specifically teaches amplification without prior isolation in fruit flies and blood flukes, Grevelding also specifically suggests amplification in other eukaryotic organisms, which would necessarily include mammalian cells. Grevelding also particularly points out that since the organisms used in the method are coated with a cuticle and tegument, one of skill would reasonably expect that the method would work for other types of cells. The motivation statement above has been modified accordingly to address the amendments to the claims. Therefore, Applicant's arguments are not persuasive and the rejections are maintained.

Applicant traverses the rejection of claims as being obvious over Dauer, Grevelding and Ughelstad or in view of Dzieglewska. Regarding Ughelstad, Applicant argues effectively that Ughelstad does not cure the deficiencies in Dauer and Grevelding. These arguments are not persuasive for the reasons stated above.

Regarding Dzieglewska and claims 11 and 17, Applicant argues that Dzieglewska teaches amplification which requires lysis and that it does not cure the deficiency in Dauer and Grevelding. While Applicant's arguments are noted, in response it is noted that Dzieglewska is relied upon only for a teaching of specific diameter of magnetic beads. The amplification steps that may be taught do not teach away, in any way, from the use of particular diameter beads in the method of Dauer, Grevelding and O'Neill (as amended). Therefore, while Applicant's arguments are moot, the rejections are maintained.

Finally, Applicant traverses the rejection of claims as being obvious over Dauer, Grevelding and Inuma. Applicant argues that when the disclosures are considered "as a whole", Applicant notes that Inuma teaches separation of cells using immuno magnetic separation. While Applicant's arguments are noted, Inuma is relied upon only for rendering obvious that the claims can be applied to a variety of target cells, including leukocytes obtained from blood cells. While Applicant is correct that Inuma teaches isolation using immuno-labeling of magnetic cells, Applicant is not considering the teachings of Dauer, which teaches isolation without specific labeling. Therefore, when considered together, in combination, it would have been obvious to apply the technique of Dauer and Grevelding to the isolation of a variety of cell types, including leukocytes as taught by Inuma. Finally, Applicants arguments that Inuma does not cure deficiencies in Dauer and Grevelding have been considered but are not persuasive for the same reasons as asserted above. Applicant's arguments are not persuasive and the rejections are maintained.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Hardingham et al. (Cancer Research, 1993, vol. 53, p. 3455-3458) teaches a general method for immunobead isolation of circulating tumor cells followed by PCR (Abstract).

No claims are allowed. All claims stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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